IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants	:	Ivan KING and Li-Mou ZHENG
U.S. Serial No.	:	10/738,423
Confirmation No.	:	8783
Filed	:	December 16, 2003
Art Unit	:	1633
Examiner	:	Qian Janice Li
For	:	COMPOSITIONS AND METHODS FOR TUMOR-TARGETED DELIVERY OF EFFECTOR MOLECULES

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March 12, 2009

Commissioner for Patents
P.O. Box 1450
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Sir/Madam:

APPELLANT REPLY BRIEF TO EXAMINER'S ANSWER PURSUANT TO 37 CFR § 1.193

An Examiner's Answer was mailed on February 5, 2009. Appellant may file a Reply Brief to the Examiner's Answer within two months from the date of the Examiner's Answer. Accordingly, this Reply Brief is timely filed. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

REPLY BRIEF

This Reply Brief is filed in response to the Examiner's Answer mailed February 5, 2009. Claims 113, 115-117, and 119-124 are currently under appeal. Independent claim 113 is drawn to a method of inhibiting the growth of a solid tumor cancer, comprising administering to a subject an effective amount of cytoxan or cisplatin and an effective amount of a pharmaceutical composition comprising an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises a msbB$^-$ mutant. The present specification discloses a mutant msbB$^-$ *Salmonella* strain VNP20009 (page 74, lines 8-9), and the uses of strain VNP20009 together with cytoxan or cisplatin (page 104, line 1 to page 106, line 20). Dependent claims 115-117 define the solid tumor or cancer, and the subject (a mammal or a human). Dependent claim 119 specifically delimits the claim to administration of an effective amount of cisplatin. Dependent claims 121-122, which are duplicates, specifically delimit the method of claim 115 to a lung cancer.

Independent claim 123 is drawn to a method of inhibiting the growth of a solid tumor cancer, comprising administering to a subject an effective amount of an anti-cancer compound and an effective amount of a pharmaceutical composition comprising an attenuated tumor-targeted *Salmonella*, wherein the *Salmonella* comprises a msbB$^-$ mutant. The present specification discloses a mutant msbB$^-$ *Salmonella* strain VNP20009 (page 74, lines 8-9), and the uses of strain VNP20009 together with an anti-cancer compound (page 104, line 1 to page 106, line 20). Dependent claim 124 specifically delimits the claim to administration of an effective amount of cisplatin.

35 U.S.C. 103(a) Rejection

Claims 113, 116, 117, 119, 120, 123, 124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Low et al. (Nat. Biotech. 17:37-41 (1999)) in view of Schachter et al. (Cancer Biother. Radiopharm. 13:155-64 (1998)).

This rejection, as stated in the Final Office Action of December 20, 2007 remains the main thrust of the Examiner's argument. The Examiner's Answer repeats such arguments.

Responses to Arguments

Reasonable Expectation of Success or Anticipated Success: Predictability

Applicants' maintain the first and primary argument of their Appeal Brief, which is that "the Examiner's stated rationales fail to articulate grounds for a reasonable expectation of success or anticipated success." The Examiner states: "the bacteria therapy has been proven effective in treating melanoma as taught by *Low et al.*, and the cisplatin has been proven effective in treating melanoma as shown by *Schachter et al.*": therefore "it would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for the treatment of melanoma with a reasonable expectation of success." *See* page 10 of the Examiner's Answer. The Examiner's belief is that where one therapy is successful, and another general category of treatment is successful, a combination of the two will always be *prima facie* obvious. The Examiner's position is that there will naturally be a reasonable expectation of success in any such combination.

In support of this point, the Examiner cites the case of *In re Kerkhoven,* 205 USPQ 1069 (CCPA 1980), remarking that such case stands for the proposition that "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art."

The Examiner's literal reading of case law such as *In re Kerkhoven,* which involved combinations of spray-dried detergents, ignores the fact that the technologies in the prior art, as well as the combination of the present application, are not simplistic elements but instead are each modulators of complex immunological interactions – interactions which may adversely affect overall effectiveness of treatment, and which lead to unpredictability in the art. As Applicants stated in their Amendment in Response to the December 14, 2006 Final Office Action, p. 12, "the technical art dealt with in Kerkhoven is a far more predictable one than in the present case. For example, mixing

two detergent compositions to form a third effective detergent composition has a far greater expectation of success than developing an effective combination cancer therapy."

The Applicants further provided evidence of the unpredictability in the art with the aforementioned responsive document by making available three separate scientific abstracts or reports showing unpredictability in the chemotherapeutic arts respecting combinations. The first[1] provides data demonstrating that the known anticancer drug Ara-C, in combination with an additional anticancer drug 2-CdA, provides a synergistic inhibition of cancer cell lines in vitro, but also reports that combinations of Ara-C with either fludarabine or bendamustine yielded antagonistic or additive inhibitory effects. The second[2] reports that when the anticancer drug docetaxil was combined with one of 18 additional anticancer drugs, and the drug combination was subsequently tested for effectiveness in inhibiting cell growth in 3 different prostate cell lines, certain combinations yielded synergistic growth inhibitory effects (docetaxil in combination with doxorubicin or epirubicin), antagonistic growth inhibitory effects (docetaxil in combination with cisplatin, carboplatin, or etoposide), and that other combinations yielded additive or synergistic effects (docetaxil in combination with retinoic acid, cyclosporine A, or vinorelbine). The third[3] reported that two separate anticancer compounds, perifosine and UCN-01, separately and individually added to a cell culture, were inactive in inhibiting the growth of two lung adenocarcinoma cell lines. However, when combined at the same concentration ranges, the combination almost completely inhibited cell growth. These examples demonstrate that combinations of anti-tumor agents may work synergistically, antagonistically, or may act without any measurable effect. Thus, contrary to the Examiner's assertion, it is not obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose.

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1 Chow et al., Jan. 2003, "In AML cell lines Ara-C combined with purine analogues is able to exert synergistic as well as antagonistic effects on proliferation, apoptosis and disruption of mitochondrial membrane potential." Leuk. Lymphoma 44(1): 165-73. [Abstract only]

2 Budman et al., Nov. 2002, "Synergistic and antagonistic combinations of drugs in human prostate cancer cell lines in vitro." Anticancer Drugs. 13(10):1011-6.

3 Dasmahatrapatra, et al., Aug. 1, 2004, "*In vitro* Combination Treatment with Perifosine and UCN-01 Demonstrates Synergism against Prostate (PC-3) and Lung (A549) Epithelial Adenocarcinoma Cell Lines," Clinical Cancer Research, 10:5242-5252.

Given the level of unpredictability in the art, there also would not have been a reasonable expectation of success when combining two treatments, especially an infectious agent and an immune-dampening chemotherapy. The Examiner, with respect to the particular technology claimed, has failed to articulate grounds for a reasonable expectation of success or anticipated success.

As set forth by the Examiner, the analysis under *In re Kerkhoven* fails to even acknowledge that the USPTO recognizes circumstances which render combinations of two compounds or compositions nonobvious, even though each shows efficacy with regard to the compounds' stated purpose, for example, where synergism is demonstrated. *See Merck & Co., Inc., v. Biocraft Labs, Inc.* 874 F.2d 804, 806 (1989) (where a combination of two diuretics, amiloride and hydrochlorothiazide, was originally held to be non-obvious but had been allowed after presentation of evidence allegedly demonstrating a synergism produced by the combination).

During prosecution, Applicants' demonstrated that such synergism existed. In an Amendment to the December 14, 2006 Final Office Action, Applicants argued that *Schacter et al.* recited a combination of chemotherapeutic drugs which provided an overall response rate of 44%. They then used the cytokine "biotherapy", consisting of IFN-α and GM-CSF, increasing the response rate to around 50%, which only marginally enhanced the effect of the drug combinations. Applicants then showed that synergism exists with regard to one present combination of the attenuated tumor-targeted Salmonella: whereas administration of the chemotherapeutic drug cytoxan in the absence of attenuated tumor-targeted Salmonella provided only a marginal reduction in tumor volume, and whereas tumor-targeted Salmonella alone showed a reduction of approximately 50%, when both cytoxan and Salmonella were used in combination, the decrease in tumor volume was around 80%. Applicants argued that if the effects had been merely additive, tumor reduction would have only approached 55-60%. Moreover, synergism of this particular combination (of the attenuated tumor-targeted Salmonella and cytoxan) is evidenced by the fact that when the attenuated tumor-targeted Salmonella was combined with another chemotherapeutic drug (mitocin C), no synergistic effect was demonstrated.

Reasonable Expectation of Success or Anticipated Success: Counterintuitive Combination

In addition to the arguments made above, a lynchpin of the Applicants' argument has been that to combine a bacterial therapy for the treatment of cancer with a chemotherapy known to weaken the immune system of chemotherapy patients would not only not have been *prima facie* obvious at the time of invention, but would have been counterintuitive. In this vein, Applicants' have also made attempts to show that the Examiner's simple categorization of the bacterial treatment as a "biotherapy" akin to the cytokine treatment disclosed in *Schachter et al.* is misplaced.

As Applicants' pointed out in their Supplemental Amendment in Response to the December 14, 2006 Final Office Action, "Proceeding contrary to accepted wisdom is evidence of nonobviousness." MPEP 2145(X.D.3). As was stated in that Supplemental Amendment, "In contrast to Examiner's conclusion it is respectfully submitted that Appellants' use of tumor-targeted bacteria in a combination chemotherapy regimen goes against commonly accepted thinking in the chemotherapy arts. It is known that chemotherapy often results in a severe decrease in neutrophils, a condition known as neutropenia. A major result is a severely compromised ability of the cancer patient to fight infection against bacterial and fungal pathogens. [Citation and exhibit omitted.]"

The Examiner's Answer indicates that the above argument was found non-persuasive. The Examiner's reply is as follows:

> ... almost each of chemotherapeutic compounds in cancer therapeutic regimen would weaken a patient's immune system individually, but weighing the pros and cons, the skilled artisan still combine multiple compounds for the need of combating hard to kill tumor cells, it is a matter of balancing the beneficial and damaging effects of an anti-cancer drug regimen. *Low et al.* clearly teaches that the mutant strain of *Salmonella* was attenuated by auxotrophic mutations that would limit their pathogenesis in normal tissues but retained the high-level replication in a tumor-selective manner following systemic administration. Apparently, *Low et al.* was aware of the potential hazard using *Salmonella* in cancer therapy, and attempting to minimize the toxic effect while utilizing its tumor-targeting effect. Further, as shown by *Schachter*, it was within the levels of the skilled to determine the appropriate timing of drug administration in the combination therapy. For example, *Schachter et*

> *al.* did not use the biotherapy with the chemotherapy simultaneously, rather, they use such sequentially, i.e. modulating a patient immune system before or after the chemotherapy. Accordingly, it would have been within the knowledge of the skilled in the art to wisely use the newly developed bacteria therapy with a conventional chemotherapy sequentially to minimize side effects.

The Examiner further remarks upon the technology as follows:

> ... considering that the biotherapy taught by *Schachter et al.* is for priming and immune regulation, there was evidence in the prior art showing that attenuated *Salmonella* also have priming and immune regulation effect. *Jirillo et al.* (Int J Immunopharmacol 1986;8:881-6) teaches that attenuated *Salmonella* bacteria enhance immune responsiveness in patients with gynecologic malignancies via immune regulation (see e.g. the abstract). Thus, attenuated *Salmonella* taught by *Low* has similar underlying principle as does the biotherapy taught by *Schachter* in treating cancer. Accordingly, it was not counterintuitive for the skilled to combine the bacteria therapy with the conventional therapy when used with caution.

Applicants believe that the above characterization of the Examiner belies a fundamental misunderstanding with respect to the method of action of the attenuated tumor-targeted Salmonella, as well as a lack of understanding of the teaching in *Jirillo,* and that this misunderstanding leads the Examiner to believe that the attenuated tumor-targeted *Salmonella* is a "biotherapy" akin to and interchangeable with that of *Schachter et al.* The attenuated tumor-targeted *Salmonella* **does not** follow the same underlying principle as does the biotherapy taught by *Schachter.*

The "biotherapy" of *Schachter et al.* consists of the cytokines GM-CSF and IFN-α. Indeed, both of these cytokines act by enhancing immune responsiveness, through myelorestorative action, and immunomodulatory effect[4]. Please note that as stated in footnote number 4 below, one of the functions of GM-CSF is to promote the production of certain blood cell lineages, such as

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4 *See Schachter et al.*, p. 156, stating, "[Interferon α] main mode of immunomodulatory action – in addition to direct tumoricidal effect – is via enhanced natural killer (NK) and cytotoxic T-lymphocyte activity (CTL) and by augmentation of tumor-associated (TAAs) and histocompatibility (HLA or MHC) antigen expression *in vivo*. While the anti-tumor activity of IFNα is optimal at high doses, its immunomodulatory activity is optimal at intermediate, more physiological and less toxic doses. GM-CSF is a multifunctional cytokine, which can promote the production of several blood cell lineages, its predominant targets being monocytes, neutrophils and their precursors. *Schachter et al.* then further states "Published data indicate that low dose GM-CSF, while associated with los toxicity – has shown some myelorestorative, *but mainly immunomodulatory* effect of activating Peripheral Blood Monocytes (PBMO)." [Emphasis added]

neutrophils, i.e. the same cells identified above as being depleted during chemotherapy. Thus, the cytokine therapy's function is at least partially restorative.

Jirillo, likewise, addresses cancer-related immunodeficiencies by positing "a possible role for lipid A in the treatment of gynecologic cancer-related immunodeficiency." *See Jirillo* p. 884. Said Lipid A is a moiety of bacterial lipopolysaccharide (LPS). As *Jirillo* states, while lipid A may act as a modulator of the immune system, it also exerts negative general effects such as "pirogenicity, lethal toxicity, Shwartzman reaction etc." *Id.* In *Jirillo*, a modified bacteria retaining lipid A is being used to boost immune competence; it is precisely the immune stimulatory effects of lipid A which are being tested.

The independent claim of the present application recites "an attenuated tumor-targeted *Salmonella*, wherein the Salmonella comprises an msbB$^-$ mutant." The msbB$^-$ mutation specifically results in an inactivated lipid A. This mutation was introduced so as to minimize what was seen to be the harmful immune response of the *Salmonella* bacteria caused by the presence of Lipid A (lethal toxicity, cytokine TNFα-induced septic shock),[5] whereas *Jirillo*, in contrast, is utilizing a bacteria with lipid A, despite its harmful effects, to activate the immune system to response.

Thus, the Examiner's contention that the present tumor-targeted attenuated *Salmonella* is being used to prime the immune system, just as the bacteria in *Jirillo* does, thereby making it equivalent to the stimulatory cytokines of *Schachter et al.*, is false.

While the Examiner states that "*Low et al.* was aware of the potential hazard using *Salmonella* in cancer therapy, and attempting to minimize the toxic effect", this does not render the introduction of a combination therapy of said bacteria, and a chemotherapeutic agent causing chemotherapeutic

5 *See* the specification of the present application, p. 10: "Modifications to the lipid composition of tumor-targeted bacteria which alter the immune response as a result of decreased induction of TNFα production were suggested by Pawelek *et al.* (Pawelek *et al.*, WO 96/40238). [...] In *Escherichia coli*, the gene *msbB* (*mlt)* which is responsible for the terminal myristalization of lipid A has been identified [citations omitted]. Genetic disruption of this gene results in a stable non-conditional mutation which lowers TNFα induction."

immunosuppression obvious. The Examiner also stated that *Low et al.* "concluded that [the results [of their animal *in vivo* and human *in vitro* experiments]] "Have been consistent with the notion that the msbB$^-$ bacteria can be safe for use in humans," but the Examiner presents no evidence to show obviousness regarding safety, efficacy, or predictability of result *in this instance, in this particular combination with said chemotherapy.*

It is precisely this confusion in the state of the art regarding the beneficial or detrimental role of bacterial lipid A in the chemotherapeutically immunosuppressed which itself demonstrates that there existed conflicting ideas about what would be effective and ineffective in cancer treatment, demonstrates the inconclusive nature of what would have been considered safe, demonstrates unpredictability in the art, and also demonstrates that there was not a reasonable expectation of success in the art at that time so as to render the combination obvious.

35 U.S.C. 103(a) Rejection

Claims 115, 121, and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Low et al. (Nat Biotech 17:37-41 (1999)) in view of Schachter et al. (Cancer Biother Radiopharm 13:155-64 (1998)), **further in view of** *Pawelek et al.* (Cancer Res. 1997; 57:4537-44). *See* Page 8 of the Examiner's Answer.

The article by *Pawelek et al.,* is implicated in the new ground of rejection as follows: according to the Examiner, while *Low et al.* in view of *Schachter et al.* illustrated the tumor-suppressing effect of attenuated *Salmonella* on melanoma, but not particularly on lung or colon cancer, *Pawelek et al.* corrects this deficiency by establishing that it was well known in the art that the attenuated *Salmonella* is capable of targeting multiple tumors, including colon and lung carcinoma, while also supplying the basis for the proposition that it was well known in the art that a chemotherapeutic compound such as cisplatin has been a commonly used compound for treating a wide variety of solid tumors, including lung and colon cancer.

Applicants wish to respond that all arguments made above respecting *Low et al.* and *Schachter et al.* are applicable to the obviousness rejection including *Pawelek et al.* As was stated in Applicants' Appeal Brief of October 9, 2008 with regard to the rejection over *Schachter et al.* and *Low et al.*, the Examiner's newly stated rationale fails to articulate grounds for a reasonable expectation of success or anticipated success beyond conclusory statements, such as the following: "the skilled was[sic] constantly searching for new means to improve conventional cancer treatment, and given that each of the cited references teaches an agent that is effective in cancer therapy, one would have had a reasonable expectation of success when combining the two." *See* Examiner's Answer, p. 8.

Applicants herein also note each of the foregoing points made in this Reply Brief apply to the *Pawelek et al.* reference. Indeed, the unpredictability of the art of treating lung and colon carcinomas would be a similarly unpredictable to the treatment of melanoma, and certainly more unpredictable than is predicated by the Examiner's analysis of the relevant case law. Again, a person of ordinary skill in the art would not have had a reasonable expectation of success with respect to the combination of *Low et al., Schachter et al.,* and *Pawelek et al.* The above arguments which apply to the mischaracterization of the attenuated tumor-targeted *Salmonella* as a biotherapy akin to that disclosed in *Schachter et al.*, and which argue that the combination is contrary to conventional wisdom in the art would apply no less to the combination as used to treat lung and colon carcinomas as it would melanoma.

In summary, Applicants' submit that the Examiner has not made a legally or factually sufficiently claim of obviousness under 103(a), and that Applicants' have sufficiently rebutted all claims to alleged obviousness over the prior art. Applicants thus respectfully request allowance of the present application.

Respectfully submitted,

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